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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/19, 31/557

A1

(11) International Publication Number: WO 99/20266

(43) International Publication Date: 29 April 1999 (29.04.99)

(21) International Application Number: PCT/US98/21631

(22) International Filing Date: 20 October 1998 (20.10.98)

(30) Priority Data:
08/954,122 20 October 1997 (20.10.97) US

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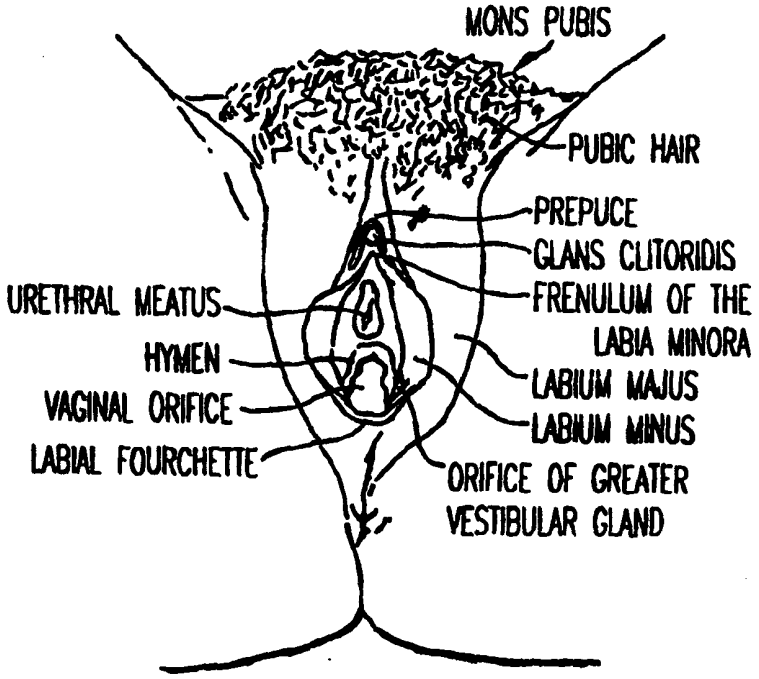
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHODS, COMPOSITIONS, AND KITS FOR ENHANCING FEMALE SEXUAL DESIRE AND RESPONSIVENESS

(57) Abstract

Topical application of a prostaglandin directly to the clitoris is effective for enhancing female sexual desire and responsiveness.



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TITLE OF THE INVENTION

METHODS, COMPOSITIONS, AND KITS FOR ENHANCING FEMALE SEXUAL DESIRE AND RESPONSIVENESS

This application is a continuation-in-part of U.S. patent application serial number 08/954,122 filed October 20, 1997.

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to methods for enhancing female sexual desire and responsiveness. The present method also relates to compositions and kits useful for enhancing female sexual desire and responsiveness.

Discussion of the Background:

The female sexual response cycle can be divided into the four following phases (as adapted from Diagnostic and Statistical Manual IV, "Sexual and Gender Identity Disorder," American Psychiatric Association. Washington, D.C., pp. 493-494 and 735-751, 1994:

1. Desire, which includes fantasies about sexual activity and the desire to have sexual activity;

2. Excitement, which consists of subjective senses of sexual pleasure and accompanying physiological changes including vasocongestion in the pelvis, vaginal lubrication, and expansion and swelling of the external genitalia;

3. Orgasm, which consists of peaking of sexual pleasure with release of sexual tension; and

4. Resolution, which consists of a sense of muscular relaxation and general

well-being.

Disorders of female sexual desire or response are estimated to affect from 30 to 50 percent of the adult population in various studies (see, *e.g.*, S. G. Nathon, "The Epidemiology of the DSM-III Psychosexual Dysfunctions," J. of Sex and Marital Therapy, vol. 12, no. 4, pp. 267-281 (1986); Diagnostic and Statistical Manual IV, "Sexual and Gender Identity Disorder," American Psychiatric Association, Washington, D.C., pp.493-539, 1994; M. Osborn et al, "Sexual dysfunction among middle aged women in the community," British Medical Journal, vol. 296, pp. 959-962 (1988); E. Frank et al, "Frequency of Sexual Dysfunction in "Normal Couples"," New England Journal of Medicine, vol. 299, pp. 111-115 (1978); and K. Garde et al, "Female sexual behavior: a study in a random sample of forty-year-Old Danish Women," Maturitas, vol. 2, pp. 225-240 (1980)). These very common disorders may have a variety of causes including psychogenic etiologies, anatomical disorders, drug-induced disorders, diabetes mellitus, post-surgical disorders, atherosclerosis, post-traumatic disorders, as well as endocrine etiologies. The terms disorder and dysfunction are used interchangeably in this application.

The search for effective pharmacologic treatments to influence sexual behavior has been a preoccupation of all societies throughout history (see, *e.g.*, E. L. Abel, Psychoactive Drugs and Sex, Plenum Press, New York, 1985; and J. Buffum, "Substance abuse and high-risk sexual behavior," J. Psychoact. Drugs, vol. 20, pp.165-168 (1988)). In one of the few scientific review articles on this topic (R. C. Rosen et al, "Prosexual Drugs: Empirical Status of the "new Aphrodisiacs"," Archives of Sexual Behavior, vol. 22(6), pp.521-543 (1993)), Rosen states: "In particular, the search for the perfect aphrodisiac - a drug that will heighten sexual desire, pleasure and performance has been a continuing cultural quest from ancient to modern times. Natural substances such as datura, belladonna and henbane were key ingredients in the sexual orgies of ancient fertility cults. Yohimbine has long been used by the natives of Africa to enhance their sexual prowess, as was the mandrake plant in medieval Europe (E. L. Abel, Psychoactive Drugs and Sex, Plenum Press, New York, 1985). Oysters, ginseng and Vitamin E have similarly been recommended at various times as possessing aphrodisiacal qualities (R. C. Rosen et al, Sexuality, Random House, New

York, 1984). Given the perennial search for an effective aphrodisiac, it is surprising that relatively few drugs have been demonstrated to have specific prosexual properties."

L-dopa has been reported to stimulate sexual responsiveness in male and female patients. However, subsequent studies have yielded inconsistent or contradictory results regarding the effect of L-dopa on sexual behavior (M. Hyppa et al, "Is L-dopa an aphrodisiac in patients with Parkinson's disease?," in Sexual Behavior Pharmacology and Biochemistry, M. Sandler et al, Eds., Plenum Press, New York, 1975; and O. Benkert et al, "Effect of L-dopa on sexually impotent patients," Psychopharmacologia, vol. 23, pp. 91-95 (1972)). Most of these studies deal exclusively with men and extremely few studies have even mentioned women. Apomorphine has been investigated for erectile dysfunction in men, but there have been no positive reports in women. Nomifensine and bupropion which are atypical anti-depressants acting on dopamine have been reported to have stimulatory effects on females with decreased sexual desire (S. Lal et al, "Apomorphine induced penile tumescence in impotence patients - preliminary findings," Prog. Neurol. Psychopharmacol. Biol. Psychiat., vol. 11, pp. 235-242 (1987). Subsequent studies by Klein et al did not replicate these effects (K. B. Klein et al, "Drug treatment of patients with inhibited sexual desire: A controlled clinical trial," presented at the SSTAR annual meeting, New Orleans, 1987).

An oral formulation of phentolamine is reportedly being investigated for efficacy in treating female sexual dysfunction by Zonagen (Woodlands. Texas) according to information on their website. No results of any such study are currently available.

U.S. Patent No 5,731,339 discloses the use of oral phentolamine as a possible treatment for male erectile dysfunction and for female sexual dysfunction. Reports at the recent Annual Meeting of the American Urological Association indicate that oral phentolamine may benefit only 20-30% of men suffering from mild erectile dysfunction (see Goldstein, I. et al, Abstract #919, The Journal of Urology, V. 159(5), May 1998, 240.)

Sildenfil is reputed to be under investigation in Europe by Pfizer as a possible

oral therapy for female sexual dysfunctions. No published results are available, and representatives of Pfizer have warned that sildenfil is not known to be either safe or effective in women.

The oral administration of sildenafil as disclosed in U.S. Patent No 5,270,323 to enhance erections has recently been approved by the FDA and extensively reported in the media. Sildenafil is thought to act by inhibiting the destruction of cyclic GMP in the penis by a specific phosphodiesterase. The limited clinical experience with sildenafil does not allow us to know how effective it may be in general use. It may provide a benefit for 40% of a general population of men with erectile dysfunction. There are widespread concerns about the long-term safety of sildenafil in the general population and recent reports of sudden death in men using it.

U.S. Patent No. Re 35,752 discloses the oral administration of hydroiodic acid as a reputed method of enhancing female sexual response, and a single example of the response is given. The Tenth Edition of the Merck Manual under citation # 4678 for hydroiodic acid states: "Caution: strong irritant." No other published reports of the safety or efficacy of hydroiodic acid for enhancing female sexual response are available.

NexMed, Inc. and Harvard Scientific, Inc. have both announced in press releases that they are undertaking projects to determine whether topical administration of prostaglandin E1 may be effective in the treatment of female sexual dysfunctions.

U.S. Patent No 5,718,917 discloses the use of a meatal dose of lyophilized PGE-1 for erectile dysfunction. Reports from the previously cited AUA Meeting showed only preliminary reports with no evaluation of possible efficacy (unpublished results from discussion at The International Society on Impotence, AUA 93rd Annual Meeting, May 30, 1998).

Prostaglandins may have a possible role in human ovulation (G. M. Craig, "Prostaglandins in reproductive physiology," PMJ, vol. 51, pp. 74-84 (1975)). Prostaglandin E_1 (PGE-1), prostaglandin E_2 (PGE-2), and prostaglandin $F_{2\alpha}$ (PGF-2α) cause uterine contraction in women. Indeed, PGE-2 is presently used in the United States for inducing labor and cervical ripening.

Present therapies for disorders of sexual response and desire include various

types of psychotherapeutic counseling (J. LoPiccolo et al, "Treatment of Sexual Dysfunction," J. of Counseling and Clinical Psychology, vol. 54(2), pp. 158-167 (1986)). There is also a report of using electrical stimulators placed inside the vagina to induce orgasms (see: D. Boutos, "Apparatus for stimulating penile, scrotal, anal, vaginal, and clitoral tissue," U. S. Patent No. 5,571,118). Neither of these methods are particularly desirable or effective in treating these disorders.

Thus, there remains a need for a method for enhancing female sexual desire and responsiveness. There also remains a need for pharmaceutical compositions and kits useful for enhancing female desire and responsiveness.

SUMMARY OF THE INVENTION

Accordingly, it is one object of the present invention to provide novel methods for enhancing female sexual desire and responsiveness.

It is another object of the present invention to provide novel pharmaceutical compositions which are useful for enhancing female sexual desire and responsiveness.

It is another object of the present invention to provide novel kits useful for enhancing female sexual desire and responsiveness.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventor's discovery that application of a prostaglandin directly to the clitoris of a female is effective in enhancing female sexual desire and responsiveness.

BRIEF DESCRIPTION OF THE DRAWINGS

Various other objects, features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood from the following detailed description when considered in connection with the accompanying drawings in which like reference characters designate like or corresponding parts throughout the several views and wherein:

Figure 1 illustrates the human female genitalia; and

Figure 2 shows the results of a PGDH inhibition assay for palmitic acid (♦) and oleic acid (▲).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Thus, in a first embodiment, the present invention provides novel methods for enhancing female sexual desire and responsiveness. In the context of the present invention, the term enhancing female sexual desire and responsiveness includes the treatment of disorders of female sexual desire and/or response. The term disorders of female sexual desire and/or response means any disorder or dysfunction which causes a decrease in or absence of female sexual responsiveness or female sexual desire. This includes any persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity. It also includes decreases in the physiological response to sexual stimulation such as slowed or decreased erectile response of the female erectile tissues; slowed, decreased or absent lubrication of the vagina; slowed, decreased, or absent ability to have orgasms; decreased intensity of or pleasure in orgasms: frigidity; sexual aversion; and disorders of female sexual desire and response that are secondary to a general medical condition such as the menopausal or post-menopausal state, radiotherapy of the pelvis, atheroscelerosis, pelvic trauma or surgery, peripheral neuropathies, autonomic neuropathies, diabetes mellitus, and disorders of the innervation of any of the sexual organs. This term also includes substance-induced sexual dysfunction including but not limited to decreases in desire and responsiveness secondary to anti-depressants, neuroleptics, anti-hypertensives, tobacco, opiates, alcohol and any other drug found to decrease or eliminate any part of the sexual response cycle. Primary and secondary anorgasmia are included. Vaginismus (a psychologically induced spasm of the vagina) may be resistant to the present method and compositions.

Specifically, the present method involves application of a prostaglandin directly to the clitoris. Examples of suitable prostaglandins include, but are not limited to, PGE-1; PGE-2; PGE-3; PGA-1; PGB-1; PGD-2; PGE-M; PGF-M; PGH-2; PGI-2; 19-hydroxy-PGA-1; 19-hydroxy-PGB-1; PGA-2; PGB-2; 19-hydroxy-PGA-2; 19-hydroxy-PGB-2; PGB-3; 16,16-dimethyl-Δ^2-PGE-1 methyl ester; 15-deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester; 16,16-dimethyl-PGE-2; 11-deoxy-15-methyl-PGE-1; 16-methyl-18,18,19,19-tetrahydrocarbacyclin; (16RS)-15-deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester; (+)-4,5-didehydro-16-phenoxy-α-tetranor-PGE-2

methyl ester; 11-deoxy-11a,16,16-trimethyl-PGE-2; (+)-11a,16a,b-dihydroxy-1,9-dioxo-1-(hydroxymethyl)-16-methyl-*trans*-prostene; 9-chloro-16,16-dimethyl-PGE-2; arboprostil; iloprost; CL 115,347; 16,16-dimethyl-PGE-2; 15(S)-15-methyl-PGE-2; 9-deoxy-9-methylene-16,16-dimethyl-PGE-2, potassium salt; carbaprostacyclin; prostaglandin D_2; 19(R)-hydroxy-PGE-2; 13,14-dihydro-PGE-1; 11β-PGE-2; 19(R)-hydroxy-PGE-1; 11-deoxy-16,16-dimethyl-PGE-2; and semisynthetic or synthetic derivatives of these natural prostaglandins, or any derivative or any prostaglandin analog capable of acting as a vasodilator or neuromodulator. Cyclodextrin complexes are also included as they may enhance the activity of the solution and stabilize the prostaglandin. Racemic, optically enriched or purified stereoisomers of any of these compounds are also included. Physiologically acceptable salts are also included. Preferably, the prostaglandin is PGE-1, PGE-2, PGE-3, PGD-2, and CL 115,347. Most preferably, the prostaglandin is PGE-2, PGE-3, or PGE-1.

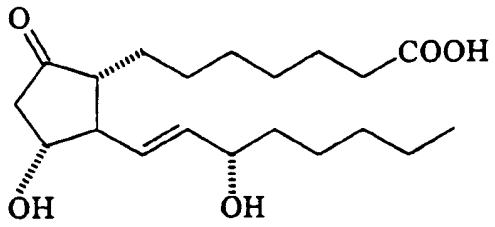
Preferably, the prostaglandin is administered topically, directly to the clitoris. The clitoris may be retracted and hidden underneath the clitoral hood in the normal unexcited state. Direct administration of the prostaglandin to the clitoris may not be possible in this situation. Therefore, the prostaglandin-containing composition may be applied to the tissues covering or surrounding the clitoris, such as the prepuce and the frenulum of the labia minora (see Figure 1) with massaging in order to achieve application to the clitoris. Administration topically to the clitoris may be accomplished by applying an amount of a liquid, gel, or solid which contains an effective amount of the prostaglandin directly onto the clitoris. In the case when the prostaglandin is contained in a pharmaceutical composition which is a liquid, the administration may be accomplished by means of a dropper or syringe. The liquid solution may also be sprayed or delivered in an aerosol onto the clitoris. When the composition containing the prostaglandin is in the form of a gel, lotion, or cream the administration may be carried out by means of a tube, brush, swab or the finger tip. Pharmaceutical compositions which contain the prostaglandin and which are in the form of a solid may be administered by placing the appropriate amount of the solid directly on the clitoris or by dusting or spraying a powder.

Although the exact amount of prostaglandin to be administered will depend on

the exact size and condition of the patient, the prostaglandin is suitably administered in an amount of 1 to 5,000 μg, preferably 20 to 2,000 μg. Specifically, when the prostaglandin is PGE-1, PGE-2, or PGE-3, the PGE-1, PGE-2, or PGE-3, is suitably administered in an amount of 1 to 5,000 μg, preferably 20 to 2,000 μg, per unit dosage.

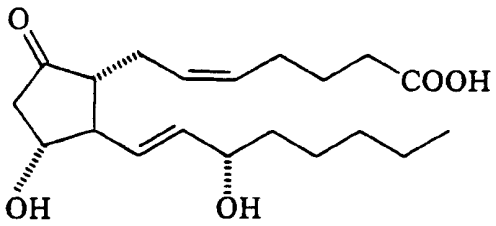
Typically, the prostaglandin will be administered 1 to 60 minutes, preferably 5 to 30 minutes, prior to the time when it is desired to commence sexual intercourse.

PGE-1, prostaglandin E_1, is also known as alprostadil or PGE_1. The formal chemical name of PGE-1 is 3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentaneheptanoic acid, and the structure of PGE-1 is



Prostaglandin E_1 may be isolated from sheep seminal vesicle tissue as described in Bergstrom et al., Acta. Chem. Scand., vol. 16, p. 501 (1962) and J. Biol. Chem., vol. 238, p. 3555 (1963). The synthesis of prostaglandin E_1 may be carried out as described in Corey et al., J. Am. Chem. Soc., vol. 91, p. 535 (1969); Corey et al., J. Am. Chem. Soc., vol. 92, p. 2586 (1970); Sih et al, J. Am. Chem. Soc., vol. 94, p. 3643 (1972); Sih et al., J. Am. Chem. Soc., vol. 95, p. 1676 (1973); Schaaf et al., J. Org. Chem., vol. 37, p. 2921 (1974); and Slates et al., Tetrahedron, vol. 30, p. 819 (1974).

PGE-2, prostaglandin E_2, is also known as dinoprostone or PGE_2. The formal chemical name of PGE-2 is 7-[3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-5-heptenoic acid, and the structure of PGE-2 is:



Prostaglandin E_2 may be isolated from sheep seminal vesicle tissue as described in Bergstrom et al., Acta. Chem. Scand., vol. 16, p. 501 (1962). Prostaglandin E_2 may be synthesized as described in Corey et al., J. Am. Chem. Soc., vol 92, p. 397 (1970); Corey et al., J. Am. Chem. Soc., vol. 92, p. 2586 (1970); and Heather et al., Tetrahedron Letters, p. 2313 (1973).

Both prostaglandin E_1 and E_2 are commercially available from Sigma Chemical Company of St. Louis, MO.

PGE-2 is also commercially available as a Prostin E-2 suppository and as Prepidil Gel from Pharmacia & UpJohn Company, Kalamazoo, MI, and as Cervidil from Forrest Pharmaceuticals, Inc., St. Louis, MO. These preparations are indicated for cervical ripening and contain between 0.5 and 20 mgs of PGE-2. No reports in the medical literature, Physicians Desk Reference, 51st Edition, Medical Economics, Montvale, NJ, 1997; or Goodman and Gillman's The Pharmacologic Basis of Therapeutics, 9th Edition, McGraw-Hill, 1996 can be found with respect to prostaglandins stimulating the human female sexual response. Indeed, in labor induction as much as 10 to 1000 times the dose effective in the present method of PGE-2 is administered to the cervix without sexual stimulation ever being reported as a side effect.

PGF-2α, prostaglandin $F_{2\alpha}$, is also known as dinoprost or $PGF_{2\alpha}$. The formal chemical name is 7-[3,5-dihydroxy-2-(3-hydroxy-1-octenyl)cyclopentyl]-5-heptenoic acid. PGF-2α may be prepared as described in U. S. patent no. 3,657,327, which is incorporated herein by reference.

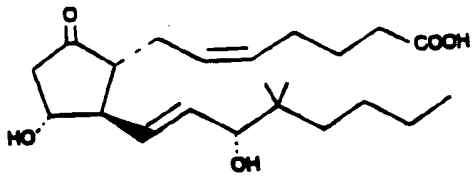
15-Deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester is also known as misoprostol and has the formal chemical name of (±)-methyl-(1R,2R,3R)-3-hydroxy-

2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate. 15-Deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester may be prepared as described in U. S. patent no. 3,965,143, which is incorporated herein by reference. Misoprostanoic acid may also be used.

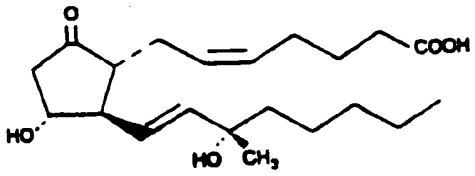
Enprostil has the formal chemical name of [1α,2β(1E,3R*),3α]-7-[3-hydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)-5-oxocyclopentyl]-4,5-heptadienoic acid methyl ester. Enprostil may be prepared as described in U. S. patent no. 4,178,457, which is incorporated herein by reference. The free acid form of enprostil may also be used.

PGI-2 is also known as prostacyclin, epoprostenol, prostaglandin I_2, prostaglandin X, PGI_2, and PGX. Prostacyclin may be prepared as described in U. S. patent no. 4,539,333, which is incorporated herein by reference.

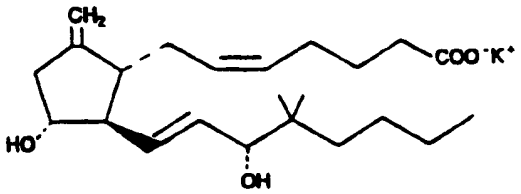
The structure of 16,16-dimethyl-PGE-2 is:



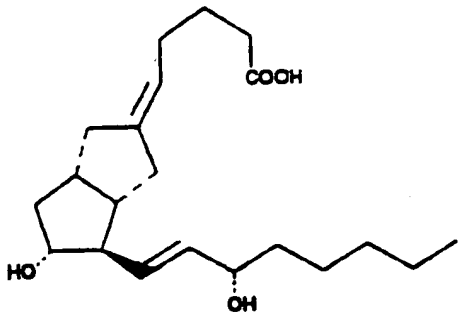
The structure of 15(S)-15-methyl-PGE-2 is:



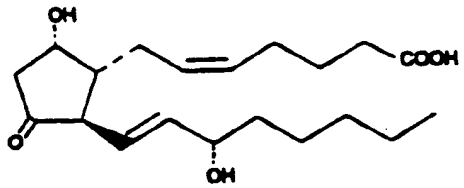
The structure of 9-deoxy-9-methylene-16,16-dimethyl-PGE-2, potassium salt is:



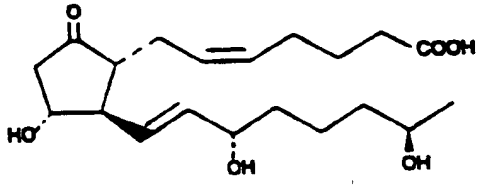
The structure of carbaprostacyclin is:



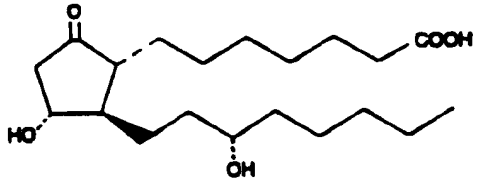
The structure of prostaglandin D_2 is:



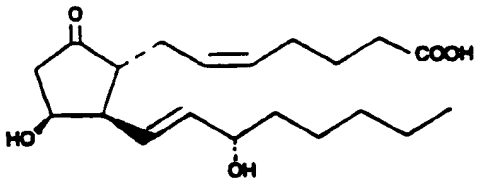
The structure of 19(R)-hydroxy-PGE-2 is:



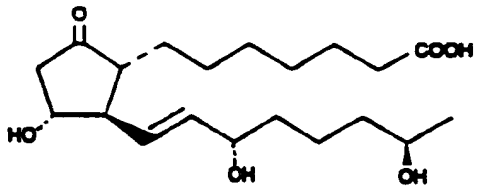
The structure of 13,14-dihydro-PGE-1 is:



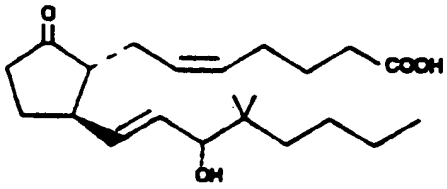
The structure of 11β-PGE-2 is:



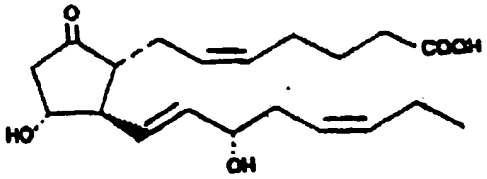
The structure of 19(R)-hydroxy-PGE-1 is:



The structure of 11-deoxy-16,16-dimethyl-PGE-2 is:



The structure of prostaglandin E_3 (PGE-3) is:



Such prostaglandins are commercially available from Cayman Chemical, Ann Arbor MI. The remaining prostaglandins are described in Alex Gringanz, Introduction to Medicinal Chemistry, Wiley-VCH, Inc., New York, pp. 158-159 and 641-642.

1997, which is incorporated herein by reference.

Cyclodextrin complexes of the prostaglandin may be used in order to increase the stability and efficacy. Cyclodextrin complexes may be prepared by adding the proper stoichiometric ratio of the prostaglandin to α, β, or γ cyclodextrin in an aqueous solvent and then either using as is or lyophilizing to provide a solid clathrate for mixing. These complexes are described in Yamamura et al, J. Chromatogr., vol. 331, pp. 383-388 (1985); Hirayama et al, Chem. Pharm. Bull., vol. 32 pp. 4237-4240 (1984); Uekama et al, J. Pharm. Sci., vol. 73, pp. 382-384 (1984); and Yamamura et al, J. Chromatogr., vol. 303, pp. 165-172 (1984), which are incorporated herein by reference.

The prostaglandin may be administered alone or it may be advantageous to simultaneously administer or to pretreat the patient with one or more co-agents to increase the efficacy of the method. Examples of co-agents which may be coadministered include:

1. Agents which inhibit 15-hydroxyprostaglandin dehydrogenase (PGDH);

2. ACE inhibitors, including but not limited to captopril, enalapril, enalaprilat, quinapril, lisinopril, and ramipril, may enhance the efficacy of the present method and decrease long term complications, such as inflammatory and fibrotic responses;

3. Nitro vasodilators, including but not limited to nitroglycerin, isosorbide dinitrate, amyl nitrate, isosorbide mononitrate, erythrityl tetranitrate, and sodium nitoprusside, may enhance the efficacy of the present method;

4. Alpha blockers, including but not limited to prazosin, phentolamine, phenoxybenzamine, dibenzamine, doxazosin, terazosin, trimazosin, tolazoline, corynthanine, rauwolscine, and piperoxan, are especially desirable for increasing the efficacy and prolonging the action of the present method;

5. Other adrenoreceptor agents, including but not limited to yohimbine, labetalol, carvedilol, and bucindolol, may also enhance the activity and prolong the action of the present method;

6. Phosphodiesterase (PDE) inhibitors, including but not limited to caffeine, aminophylline, theophylline, amrinone, milrinone, vesnarinone, vinpocetine, pemobendan, cilostamide, enoximone, peroximone, rolipram, R020-1724, zaniprast,

dipyridamole, and sildenafil, may also be effective in enhancing the efficacy of the present method and for prolonging the effect;

7. Muscarinic agents such as pilocarpine, edrophonium, and bethanacol;

8. Dopaminergic agonists such as apomorphine and bromocriptine;

9. Ergot alkaloids such as ergotamine and ergotamine analogs, including acetergamine, bravergoline, bromerguride, clanegollone, ergonovine, ergotamine tartrate, and pergolide;

10. Opiate antagonists such as naloxone, naltrexone, nalmefene, nalorphine, methyl naltrexone, CTOP, diprenorphine, β-funaltrexamine, naloxonazine, nor-binaltorphimine. natrindole, BNTX, and other analogs, which exhibit opioid antagonistic properties; and

11. Polypeptide neurotransmitters such as VIP, calcitonin, calcitonin gene related product, VIP analogs, and cholecystokinin and all its analogs such as CCK8.

12. Agents such as forskolin and and water soluble analogues that directly stimulate adenylate cyclase; dibutyryl-cyclic AMP, dibutyryl-cyclic GMP and guanylin may enhance the relaxation of cavernosal tissues by increasing the amounts of cyclic AMP and cyclic GMP.

Particularly desirable combinations are PGE and alpha-blockers, PGE and PGDH inhibitors, and PGE and PDE inhibitors. Any combinations of the single above-listed compounds or multiple combinations of different compounds or different groups may also be used. In some instances, it may be advantageous to pretreat with one or more of the co-agents. For example, pretreatment with a PGDH inhibitor followed by treatment with PGE will enhance the efficacy of the present method.

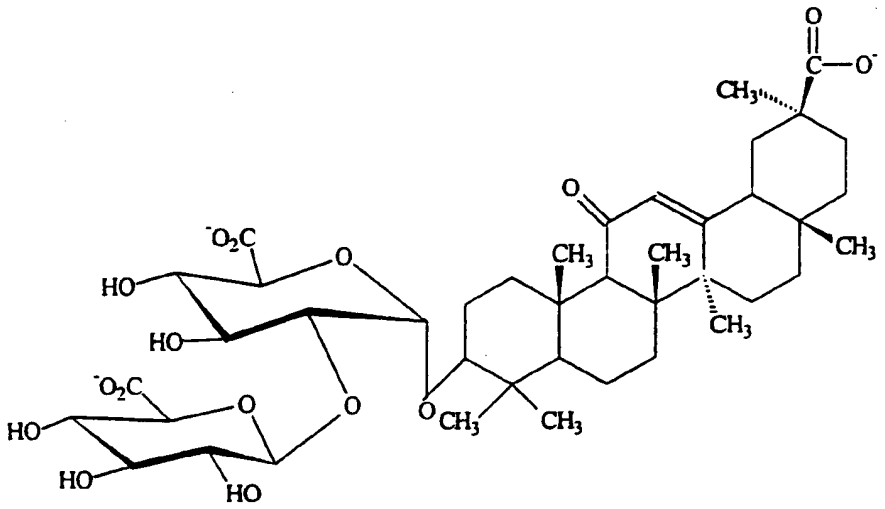
By the term "15-hydroxyprostaglandin dehydrogenase inhibitor" it is meant any compound which exhibits a significant and selective inhibition of prostaglandin degrading enzyme, or 15-hydroxyprostaglandin dehydrogenase (PGDH). Two forms of 15-hydroxyprostaglandin dehydrogenase (PGDH) are known: Type I, which is NAD^+ dependent, and Type II, which is $NADP^+$ dependent. Type I operates at a Km one order of magnitude lower than Type II and is thus more significant physiologically. Type I PGDH is described in Mak et al, Biochimica et Biophysica Acta, vol. 1035, pp. 190-196 (1990); Ensor et al, J. Lipid Mediators Cell Signalling,

vol. 12, pp. 313-319 (1995); and Berry et al, Biochemical Pharmacology. vol. 32, no. 19, pp. 2863-2871 (1983), which are incorporated herein by reference. Berry et al., Tai et al., Muramatsu et al., and Mak et al. describe assays for determining enzymatic activity of Type I PGDH as well as methods for determining the degree of inhibition of this enzyme.

Type II PGDH is described in Chang, et al, Biochem. Biophys. Res. Commun., vol. 99, pp. 745-751 (1981); Jarabak, et al, Prostaglandins, vol. 18, pp. 241-246 (1979), and Lin, et al, Biochem. Biophys. Res. Commun., vol. 81, pp. 1227-1234 (1978), all of which are incorporated herein by reference.

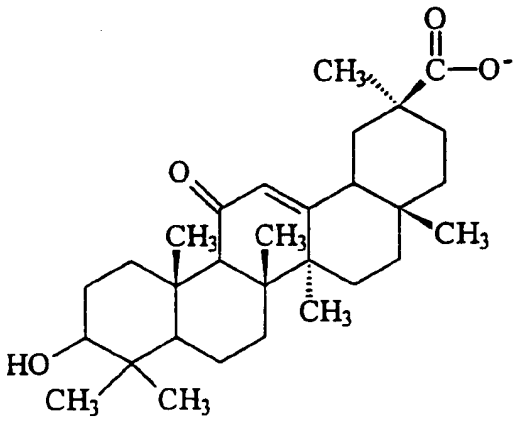
Examples of suitable 15-hydroxyprostaglandin dehydrogenase inhibitors include but are not limited to glycyrrhizic acid, licorice, glycyrrhetinic acid, various glycosides of glycrrhetinic acid, carboxenolone, DHEA, spironolactone, sofalcone, indomethacin, sulindac. etodolac. oleic acid, palmitic acid, sulphasalazine and analogues thereof, and ethacrynic acid, furosemide,chlorothiazide, hydrochlorothiazide, papaverine, cis-sulindac sulfide, trans-sulindac sulfide, cis-sulindac, trans-sulindac, glutathione thiosulfonate, divalent copper cations, divalent zinc cations, selenium, nafazatrom (Bay g-6575); lipoxygenase and cyclooxygenase-derived substrates possessing an ω-6 hydroxyl moiety such as 15-HETE, 13-HODD and HHT; gossypol, 15(R)- prostaglandin E-1, 15(R)-prostaglandin E-2, 15(R)-15-methyl prostaglandin E-2. Antibodies which bind to and inhibit either Type I or Type II PGDH may also be used.

Glycyrrhizic acid is also known as glycyrrhizin, glycyrrhizinic acid, and glycyrrhetinic acid glycoside. The formal chemical name is 20β-carboxy-11-oxo-30-norolean-12-en-3β-yl-2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid, and the structure is:



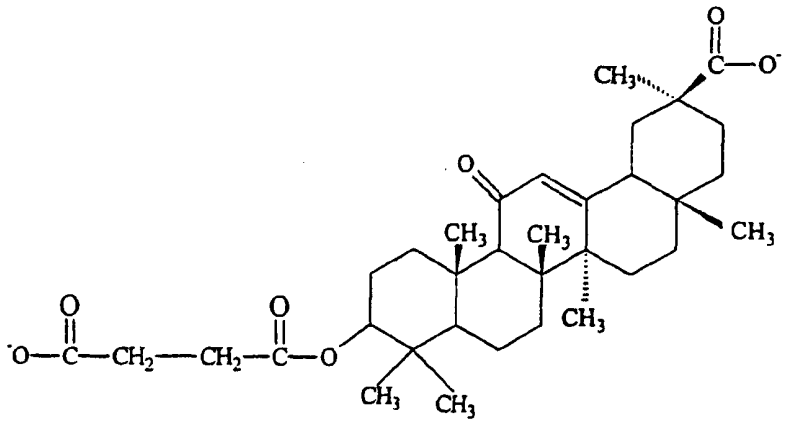
Glycyrrhizic acid is commercially available from Sigma Chemical Company of St. Louis, MO.

Glycyrrhetinic acid is unglycosylated glycyrrhizic acid, and its structure is:



Glycyrrhetinic acid may be obtained from licorice extract.

Carbenoxolone is also known as 3β-hydroxy-11-oxo-20β-olean-12-en-29-oic acid hydrogen butanedioate and has the following structure:

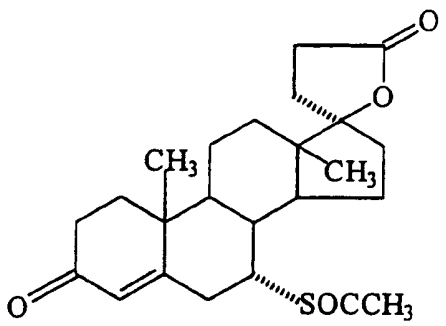


Carbenoxolone may be synthesized as described in U.S. Patent No. 3,070,623, which is incorporated herein by reference.

Licorice is also known as sweet root liquorice and glycyrrhiza and is described in the Merck Index, 10th edition, citation 4368 as "glycyrrhiza, Licorice, liquorice; sweet root. Dried rhizome and root of Glycyrrhiza glabra L., var. typica Regel & Herder (Spanish licorice), or of G. Glabra L., var. glandulifera (Waldst. & Kit.) Regel & Herder (Russian licorice), or of other varieties of G. g yielding a yellow and sweet wood, Leguminosaw. Habt. Southern Europe to Central Asia. Constit. 6-14% glycyrrhizin (the glucoside of glycyrrhetic acid), asparagine, sugars, resin."

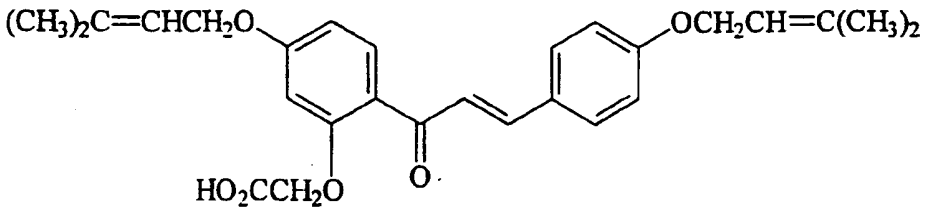
Licorice is a crude preparation prepared from dried rhizomes or roots and as such contains large numbers of compounds many of which are not identified. A simple aqueous extract of a commercially available dried licorice root preparation may be prepared as follows. Two grams of this dried licorice root was mixed with 10 mls of distilled water, stirred until thoroughly mixed at room temperature and filtered to remove particulate matter. This simple aqueous extract of licorice is effective in inhibiting PGDH and may be used as is in the present invention.

Spironolactone is also known as Aldactone A or Verospiron. The formal chemical name of spironolactone is 17-hydroxy-7-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic and γ-lactone, 7-acetate, and the structure is:



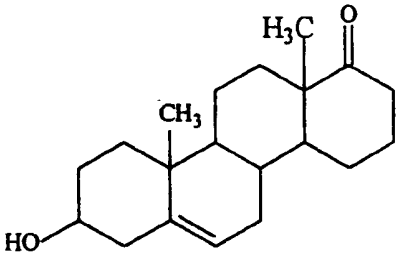
Spironolactone is commercially available from Sigma Chemical Company of St. Louis, Mo.

Sofalcone is formally known as [5-[(3-methyl-2-butenyl)oxy]-2-[3-[4[(3-methyl-2-butenyl)oxy]phenyl]-1-oxo-2-propenyl]phenoxy]acetic acid and has the formula:



Sofalcone may be prepared as described in U.S. Patent No. 4,085,135, which is incorporated herein by reference.

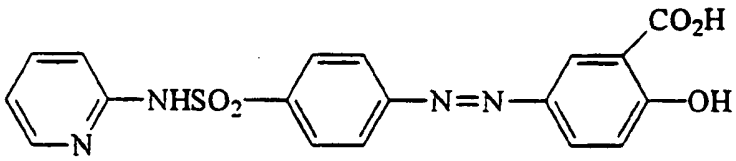
DHEA is formally known as 3-hydroxyandrost-5-en-17-one or dehydroepiandrosterone or prasterone. The structure of DHEA is:



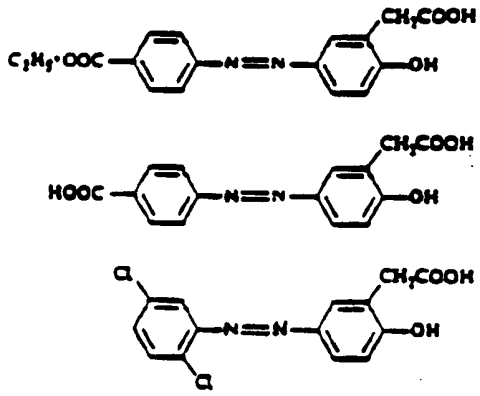
DHEA may be prepared as described in H. Hosoda et al, J. Org. Chem., vol. 38, p. 4209 (1973), which is incorporated herein by reference.

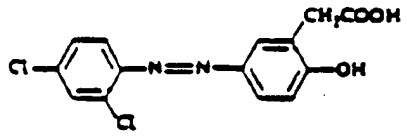
Sulfasalazine is also known as 2-hydroxy-5[[4-[(2-

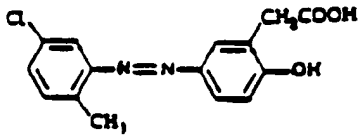
pyridinylamino)sulfonyl]phneyl]azo]benzoic acid and has the structure:

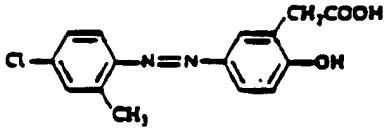


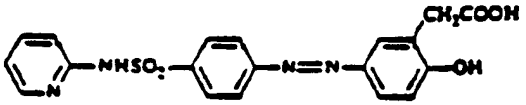
A number of sulfasalazine analogs have been shown to be inhibitors of PGDH by Berry et al, Biochemical Pharmacology, vol. 32, pp. 2863-2871 (1983). Examples of sulfasalazine analogs which may be used as the PGDH inhibitor in the present compositions include:

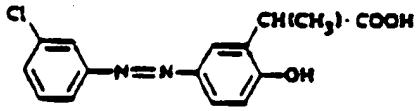


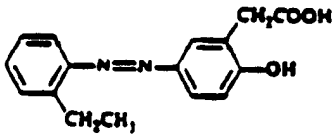


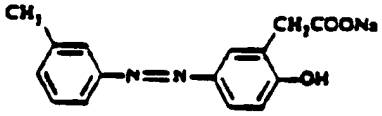


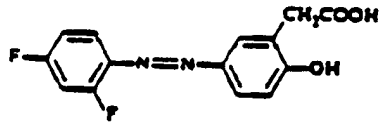


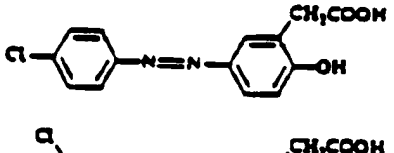


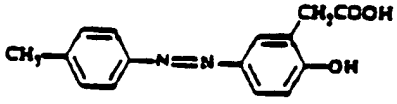


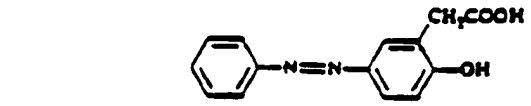


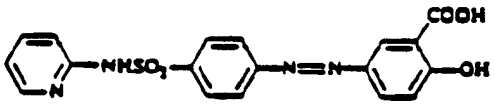


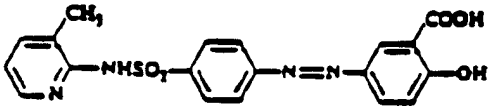


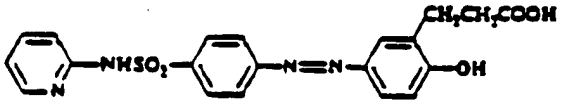


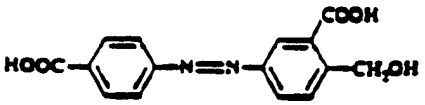


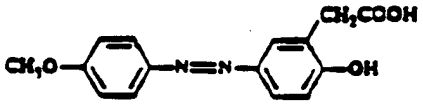


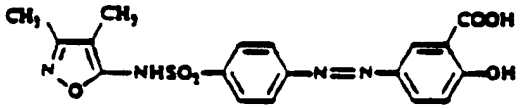


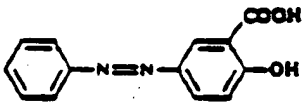


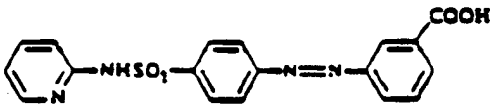










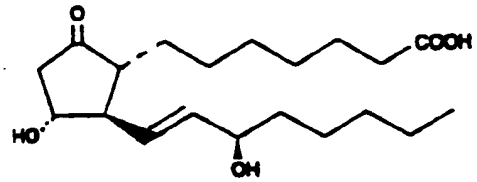


Etodolac is also known as 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. Etodolac may be prepared as described U.S. Patent No. 3,843,681, which is incorporated herein by reference.

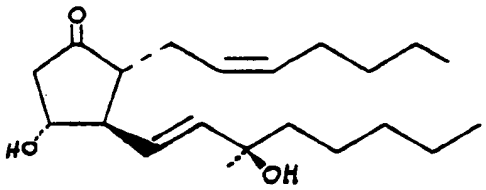
Indomethacin is also known as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. Indomethacin may be prepared as described in U.S. Patent No. 3,161,654, which is incorporated herein by reference.

Sulindac is also known as 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid. Sulindac may be prepared as described in U.S. Patent Nos. 3,654,349 and 3,647,858, which are incorporated herein by reference.

The structure of 15(R)- prostaglandin E-1 is:



The structure of 15(R)-15-methyl prostaglandin E-2 is:



Other types of 15-hydroxyprostaglandin dehydrogenase inhibitors include aliphatic and aromatic carboxylic acids. Suitable carboxylic acids particularly include any straight chain or branched, saturated, monounsaturated, or polyunsaturated aliphatic C_8-C_{31} carboxylic acid. Particularly preferred for use as component (b) in the present suppositories are free fatty acids including, but not limited to, palmitic acid, oleic acid, elaidic acid, stearic acid, capric acid, lauric acid, myristic acid, linoleic

acid, arachidic acid and arachadonic acid, all of which are commercially available from Sigma Chemical Co., St. Louis, MO.

The 15-hydroxyprostaglandin dehydrogenase inhibitor will typically be present in an amount of 25 to 100, preferably 50 to 100, pig clitoral units of PGDH inhibition activity, per unit dosage. The amount of inhibitor which corresponds to a unit of pig clitoral PGDH inhibition activity is determined using either the spectrophotometric or radio-chemical assay described in the Examples. For inhibitors which exhibit a significant absorption at 340 nm, it is preferred to use the radio-chemical assay.

In a second embodiment, the present invention provides novel pharmaceutical compositions which are useful for enhancing female sexual desire and responsiveness. The present pharmaceutical compositions are characterized as containing: (a) a prostaglandin; (b) a pharmaceutically acceptable carrier; and having a pH of 3 to 7, preferably 4 to 6. In cases in which an aqueous component is present, one may simply add a sufficient amount of a pharmaceutically acceptable acid or base, e.g., HCl or NaOH to adjust the pH to the desired value. For nonaqueous compositions, one may add to each unit dose the residual powder from 0.5 ml of a 0.01 Molar aqueous solution of a pharmaceutically acceptable citrate salt, e.g., sodium citrate, which has the desired pH. For example, 0.5 ml of 0.01 Molar sodium citrate at pH 4.5 is lyophilized, and the powdered residue is added to a unit dose of PGE-2 in polyethylene glycol (PEG) MW 1450. Upon contact of this dose with a mucosal membrane, the lyophilized citrate will dissolve and buffer the pH of the mucosal fluid to about pH 4.5 and thereby enhance the activity of the PGE-2 as the PEG pellet dissolves.

In a preferred embodiment, the present composition further comprises: (c) an antioxidant selected from the group consisting of citrate salts and tocopherol. It has been found that prostaglandins, in particular PGE-2, are especially stabile when formulated in a composition which contains a citrate salt, such as sodium, potassium, or ammonium citrate, or tocopherol. Typically, the present pharmaceutical composition will contain 1 to 2,000 μg, preferably 50 to 1,000 μg, of the citrate salt, or 20 to 2,000 μg, preferably 50 to 1,000 μg, of tocopherol. Particularly good results have been achieved when the prostaglandin is present in a 1 millimolar sodium citrate

aqueous solution or in liposomal solution which also contains 1 mg per ml of tocopherol as an antioxidant.

The present compositions may also contain the same coagents described above in the context of the present method. Thus, the present compositions may contain one or more agents which block prostaglandin degrading enzymes, one or more ACE inhibitors, one or more muscarinic agents, one or more adrenoreceptor agents, one or more dopamine agonists, one or more opiate antagonists, one or more nitrates or nitroso compounds, one or more polypeptide neurotransmitters, and/or one or more agents which inhibit phosphodiesterase.

The present pharmaceutical composition can be in any conventional form, such as a liquid, solid or gel. Examples of suitable liquids include sterile solutions, suspensions, and emulsions, including creams, ointments, and liposomes. For oil based or lipophilic preparations, other suitable anti-oxidants include BHT. For water based or hydrophilic preparations, other suitable anti-oxidants include ascorbic acid and its sodium and potassium salts. Preferred PEG suppositories contain a PEG which is solid at ambient or room temperature but rapidly dissolves/melts when placed on the clitoris. Good results have been achieved using isotonic aqueous solutions which contain sodium citrate.

Examples of suitable solids include polyethylene glycol (PEG), polyethylene oxide and other low melting point or water-soluble polymers including fatty acid esters made into suppositories or pellets. Examples of suitable gels include hydroxycellulose, gels composed of water, propylene glycol, hydroxypropyl methylcellulose and any other gels which are compatible with the prostaglandin. Liposomal mixtures are particularly preferred as they tend to induce a stronger effect at a given dose of prostaglandin and stabilize the prostaglandin. A commercially available liposome to which the prostaglandin can be added is Liposyn II™ 10 % or 20 % sold by Abbott Laboratories, North Chicago IL. The liposomes may be prepared as either anionic or cationic liposomes depending upon the prostaglandin and any co-agent present in order to maximize the desired effect. A particularly preferred gel is lecithin organogel prepared according to H. Willimann et al, "Lecithin organolgel as matrix for transdermal transport of drugs," J. Pharm. Sci., vol. 81(9), pp. 871-874

(1992). This particular preparation exhibits a dramatically enhanced potency. Examples of lipophilic liquids that are particularly preferred are triacetin, tricaprin, tricaproin, and mixtures of various triglycerides.

One may also use a gel in which one or more of the prostaglandins or co-agents is released in a controlled-released manner (i.e., released over time) to prolong the effect of the composition. For example, PGE can be formulated into a cross-linked polyethylene oxide/urethane polymer which is well tolerated by living tissues and releases the prostaglandin in a controlled release manner. Controlled release compositions are disclosed in D. H. Lewis, Controlled Release of Pesticides and Pharmaceuticals, Plenum Press, New York, 1981; and A. F. Kydonieus, Controlled Release Technologies: Methods, Theory, and Applications, CRC Press, Boca Raton, 1980, which are incorporated herein by reference.

Typically, the present pharmaceutical composition will contain the prostaglandin in a concentration such that an effective amount of the prostaglandin is delivered to the clitoris with a single application of the composition. For example, in the case of a liquid, the composition will contain sufficient prostaglandin such that an effective amount of the prostaglandin is delivered to the clitoris by application of a drop (0.01 to 0.30 ml) of the liquid. Thus, the present compositions, when in the form of a liquid will suitably contain 10 to 25,000 μg/ml, preferably 100 to 12,000 μg/ml, of the prostaglandin. In the case of a suppository, the suppository will preferably contain sufficient prostaglandin such that an effective amount of the prostaglandin is delivered to the clitoris by application of a single suppository to the clitoris. Suppositories according to the present invention typically have volumes of 0.01 to 0.30 ml, preferably 0.1 to 0.2 ml. Thus, pharmaceutical compositions according to the present invention which are in the form of a suppository will suitably contain the prostaglandin in a concentration of 10 to 25,000 μg/ml, preferably 100 to 12,000 μg/ml. Similarly, when the composition is in the form of a gel, the gel will typically contain sufficient prostaglandin such that an effective amount of prostaglandin is delivered to the clitoris upon application of a single dose (0.01 to 0.60 ml, preferably 0.05 to 0.40 ml) of the gel to the clitoris. Thus, the gels of the present invention will suitably contain the prostaglandin in a concentration of 10 to 25,000 μg/ml, preferably

100 to 12,000 μg/ml. Since drug dosages typically vary from person to person, repeated applications may be used to achieve the desired effect.

When the prostaglandin is prostaglandin E_1, E_2, or E_3, the pharmaceutical composition will suitably contain the prostaglandin E_1, E_2, or E_3 in an amount of 1 to 5,000 μg, preferably 20 to 2,000 μg, per unit dosage.

In a third embodiment, the present invention provides kits which are useful for enhancing female sexual desire and response. The present kits are characterized as containing: (a) a means for containing a prostaglandin or pharmaceutical composition containing the prostaglandin; and (b) means for administering the prostaglandin or pharmaceutical composition containing the prostaglandin to the clitoris. The means for containing the prostaglandin or pharmaceutical composition containing the prostaglandin may be a vial, a bottle, a pouch, an envelope, a can, a tube, an atomizer, an aerosol can, etc. The means for administering the prostaglandin or pharmaceutical composition containing the prostaglandin to the clitoris may be a dropper, a swab, a stick, or the nozzle or outlet of an atomizer or aerosol can. It is to be understood that the means for administering the prostaglandin or pharmaceutical composition containing the prostaglandin to the clitoris may be connected to or a part of the means for containing the prostaglandin or pharmaceutical composition containing the prostaglandin. For example, the containing means may be an atomizer or an aerosol can, and the administering means may be the nozzle or outlet of the atomizer or the aerosol can.

Examples of preferred kits include:

A. A kit which includes a container which can hold 1 to 100 unit doses of the prostaglandin or the pharmaceutical composition containing the prostaglandin and a dropper which can dispense between 0.01 to 0.6 ml as a unit dose. The container is preferably glass, metal, or a plastic known not to adsorb hydrophobic compounds.

B. A kit which includes a container which can hold 1 to 100 unit doses of the prostaglandin or the pharmaceutical composition containing the prostaglandin with a spray or aerosol applicator to spray the prostaglandin or pharmaceutical composition onto the clitoris. The container is preferably glass, metal, or a plastic known not to adsorb hydrophobic compounds.

C. A kit which includes a tube which holds 1 to 100 unit doses of a pharmaceutical composition containing the prostaglandin, which is in the form of a cream or gel, and an applicator which can dispense a unit dose of the composition.

D. A kit which includes 1 to 100 unit doses of pellets, film or suppositories containing a pharmaceutical composition comprising the prostaglandin and each individually wrapped in foil or plastic and sealed to protect the prostaglandin from the air. The foil or plastic is preferably opaque to eliminate the degrading effects of light on the prostaglandin.

E. A kit which includes 1 to 100 unit doses of a pharmaceutical composition which comprises the prostaglandin and which have been lypholized and sealed under inert gas in an ampoule or vial. Lyophilized compositions typically exhibit a much longer shelf life than other forms and may be reconstituted close to the time of use so that degradation of the prostaglandin is minimized. The kit may also include a suitable diluent, syringe and needle, and/or alcohol swabs.

F. A kit which includes 1 to 100 unit doses of a pharmaceutical composition comprising the prostaglandin and in which the unit does have been injection molded into the container for final packaging.

The present kits will also typically include means for packaging the container means and the administering means. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc. The present kits will also usually include written instructions which describe how to administer the prostaglandin or pharmaceutical composition containing the prostaglandin to the clitoris. It is to be understood that the written instructions may be on any of the container means, the administering means, or the packaging means, in addition to being present on a separate piece of paper.

Other features of the present invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

I. Formulations:

General Instructions

The composition should be sterilely prepared and stored. Prostaglandins are degraded by high temperatures. Therefore, liquid compositions should be stored between 38-45°F. Freezing and rethawing a liquid composition may degrade or inactivate the prostaglandin, so the repeated thawing of frozen compositions should be avoided. The composition should also be protected from light. The prostaglandin may have an adverse effect on children and pregnant women. So the present compositions should be kept away from children and not used by pregnant women.

The clitoris is often retracted or hidden under the clitoral hood. Thus, prior to administration of the present composition, the clitoral hood should be retracted with the finger of one hand, and the clitoral hood should be held back as the dose is applied. Alternatively, the prostaglandin-containing composition may be applied to the tissues covering the clitoris, such as the prepuce and the frenulum of the labia minora (see Figure 1) with massaging in order to achieve application to the clitoris.

A. Water-Soluble Prostaglandins, Prostaglandin Salts, and Prostaglandin Complexes

5 mg of PGE-2 is added to sterile cold water (10 ml, (+/-) 1mM in sodium citrate), stirred until dissolved and the pH adjusted with either NaOH or HCl, to a pH of about 5.4. The resulting composition was dispensed using any of the kits. For kit E, the aqueous PGE-2 solution is rapidly frozen in the vial using dry ice or liquid nitrogen and lypholized using a hard vacuum (<0.001 Torr), then covered with anhydrous nitrogen gas (other inert gases may be used), and sealed with a septum. This procedure can be used for any prostaglandin which is water soluble. Using the same procedure, fresh aqueous solutions of prostaglandin can be prepared with isotonic saline or any water-soluble compound desired. For example, lactose may be used instead of saline. PGE-1 is soluble to the extent of 80 μg/ml in water and has been used in this method of composition preparation. PGE-1 α-cyclodextrin complex and PGE-2 β-cyclodextrin complex are more water-soluble and chemically stable than either free prostaglandin, and may also be used in this method.

B. Aqueous Solutions with a Coagent

To prepare aqueous solutions of a prostaglandin and a coagent, one may combine aqueous solutions of the components in the proportion necessary to give the final desired concentration or add the desired aqueous diluent to the pure components and mix. For example, 1 mg of PGE-2 was dissolved in 10 ml of an aqueous solution of 1 mM sodium citrate, and then 300 mg of papaverine HCl was added. The resulting mixture was stirred until all the components dissolved. Then 15 mg phentolamine HCl were added, the mixture was stirred until all components were dissolved, and the pH of the resulting solution was adjusted to about 5.4. This solution, containing 100 μg of PGE-2, 30 mg of papaverine, and 1.5 mg of phentolamine HCl per ml, may then be used in any of the compatible kits above as is or lypholized and used in Kit E. Alternatively, 1 ml of aqueous PGE-2 (1.0 mg/ml), 5 ml of aqueous 60 mg/ml papaverine HCl, 1 ml of aqueous phentolamine HCl (1.5 mg/ml), and 3 ml water may be combined and mixed to produce the same solution. As stated above in Procedure A, one may use aqueous solutions of any compatible compound. For example, isotonic saline, 1 mM sodium citrate, or isotonic lactose may also be used.

C. Liposomal Solutions

Either an aqueous or oil-based solution of the prostaglandin and a coagent can be added to a liposomal mixture of, for example: 10 gm of safflower oil, 10 gm of soybean oil, 1.2 gm of egg phosphotides, and 2.5 gm of glycerin in a final volume of 100 ml (the remainder being water). Addition of 1 mg/ml of tocopherol stabilizes the prostaglandin. Two mg of PGE-2, 10 mg of tocopherol, and 2 mg of Naloxone HCl may be added to 10 ml of this prepared liposomal solution, and the resulting mixture is stirred until all the components are dissolved. The pH of the resulting solution is then adjusted to about 5.4. This solution may then be used in any of the kits listed above or lyophilized and used in Kit E. Alternatively, liposomal mixtures of PGE-2 and coagents may be prepared as outlined in R.C. MacDonald et al, Biochem. Biophys. Acta., vol. 1061, p. 297 (1991), which is incorporated herein by reference.

Liposomal solutions are particularly favored for compounds with limited solubility in water. They also increase stability of the prostaglandin, decrease burning

sensation, and lower the dose of the prostaglandin needed.

D. Organogel Preparation

Organogels are excellent as a matrix for transdermal transport of drugs (H. Willimann et al, J. of Pharmaceutical Sciences, vol. (9), pp. 871-874 (1992). 3.0 mg of PGE-2 and 3.0 mg of prazosin HCl were dissolved in 1.0 ml of isopropyl myristate and 100 mg of soybean lecithin (high purity from Signa Chemical, St. Louis). Then, 40 µl of water were slowly added with agitation to produce a thick viscous gel. This may be used in any appropriate kit listed above. Utilization of a prostaglandin cyclodextrin complex in an organogel is particularly preferred.

E. Pellets and Suppositories

In a particularly preferred embodiment, the present invention provides novel pharmaceutical compositions which are characterized as being in the form of a suppository or pellet that may be directly applied to the clitoris and comprising:

(a) a prostaglandin vasodilator;

(b) a 15-hydroxyprostaglandin dehydrogenase inhibitor; and

(c) a base material that is solid at room temperature and releases components (a) and (b) when placed upon the clitoris.

The prostaglandin and the 15-hydroxyprostaglandin dehydrogenase inhibitor may be the same as described above.

Typically, the present composition will contain prostaglandin E_1 or prostaglandin E_2 in an amount of 1 to 5,000 μg, preferably 20 to 2,000 μg, per unit dosage. The 15-hydroxyprostaglandindehydrogenase inhibitor will typically be present in an amount of 25 to 100, preferably 50 to 100, units of PGDH inhibition activity, per unit dosage. The amount of inhibitor which corresponds to a unit of PGDH inhibition activity is determined using the methods described herein.

When the 15-hydroxyprostaglandin dehydrogenase inhibitor is a fatty acid, such as palmitic acid, oleic acid, elaidic acid, stearic acid, capric acid, lauric acid, myristic acid, linoleic acid, arachidic acid and arachadonic acid, the fatty acid will suitably be present in the suppository in an amount of from about 0.1 µg to about 20

mg, preferably from about 100 μg to about 10 mg.

When the 15-hydroxyprostaglandin dehydrogenase inhibitor is etodolac, sulindac, or indomethacin, the suppository will suitably contain the 15-hydroxyprostaglandin dehydrogenase inhibitor in an amount of 0.10 mg to 20 mg, preferably 0.5 mg to 10 mg, per unit dosage of prostaglandin.

Component (c), the base or carrier material, may be composed of any material or mixture of materials that is compatible with component (a), the prostaglandin vasodilator, and component (b), the 15-hydroxyprostaglandin dehydrogenase inhibitor, and which releases components (a) and (b) upon contact with the clitoris. Examples of materials suitable for use as component (c) which releases components (a) and (b) upon contact of the suppository with the clitoris include materials such as hydrogels which contain or are saturated with components (a) and (b).

In a preferred embodiment, component (c) is a material or mixture of materials which is compatible with component (a), the prostaglandin vasodilator, and component (b), the 15-hydroxyprostaglandin dehydrogenase inhibitor, and which results in the final composition having a melting point ranging from about 60° to about 100°F, preferably from about 70° to about 90°F.

Specific examples of suitable materials for use as component (c) include but are not limited to fatty acid esters, such as ethyl stearate, methyl stearate, isopropyl stearate, butyl stearate, and cetyl lactate; fatty acid ethers, such as laureth 9; cholesterol esters, such as cholesteryl oleate and cholesteryl palmitate ; cholesterol ethers; fatty acid diglycerides; fatty acid triglycerides; fatty acids; phospholipids; glycolipids; and sphingolipids. Ethyl stearate is a particularly preferred compound for use as component (c).

Other materials suitable for use as component (c) include polyethylene glycol (PEG). The PEG is chosen so that the suppository is a solid or semisolid at room temperature but melts/dissolves rapidly on the clitoris. Good results have been achieved using PEG with an average molecular weight of about 1450.

The suppositories of this embodiment may further comprise one or more of the same co-agents described above.

Particularly desirable compositions include alpha-blockers and/or PDE

inhibitors. Any combinations of the single above-listed compounds or multiple combinations of different compounds or different groups may also be used. In some instances, it may be advantageous to pretreat with one or more of the co-agents. For example, pretreatment with a PGDH inhibitor followed by treatment with PGE will enhance the efficacy of the present method.

Typically, the suppository will contain sufficient amounts of (a) and (b) such that administration of a single suppository is sufficient to provide the desired result. Thus, a suppository would typically contain: (a) 1 to 5,000 μg, preferably 20 to 2,000 μg, of prostaglandin E_1, or 1 to 5,000 μg, preferably 20 to 2,000 μg of prostaglandin E_2; and (b) 25 to 100 units, preferably 50 to 100 units, of the 15-hydroxyprostaglandindehydrogenase inhibitor.

In a particularly preferred embodiment, the present suppository contains 1 to 20 mg of oleic acid per each mg of prostaglandin E_2 (i.e., a 1:1 to 20:1 weight ratio of oleic acid:prostaglandin E_2). In another particularly preferred embodiment, the present suppository contains prostaglandin E_2 and palmitic acid in a palmitic acid:prostaglandin E_2 weight ratio of 1:1 to 20:1.

In a preferred embodiment, the present suppositories are characterized as having a pH of 3 to 7, preferably 4 to 6. Such suppositories may be prepared by simply adding a sufficient amount of a pharmaceutically acceptable acid or base, e.g., HCl or NaOH to adjust the pH to the desired value. Alternatively, one may add ~0.5 microliter of neat lactic acid to a ~ 30 mg suppository forming a solid preparation that releases the lactic acid on melting and brings down the pH of the clitoris to about 3.5-4.5. In a particularly preferred embodiment, one may add to each unit dose the residual powder from 0.01 to 0.5 ml of a 0.01 Molar aqueous solution of a pharmaceutically acceptable citrate salt, e.g., sodium citrate, which has the desired pH. For example, 0.5 ml of 0.01 Molar sodium citrate at pH 4.5 is lyophilized, and the powdered residue is added to a unit dose of prostaglandin E_2 in ethyl stearate. Upon placing of this dose on the clitoris, the lyophilized citrate will dissolve and buffer the pH of the clitoris to about pH 4.5 and thereby enhance the activity of the prostaglandin E_2 as the ethyl stearate pellet dissolves.

Typically, the suppository is placed upon the clitoris 1 to 60 minutes,

preferably 5 to 30 minutes, prior to the time of commencing sexual intercourse.

Of course, it is also to be understood that the prostaglandin E_1, prostaglandin E_2, or prostaglandin E_3 need not be administered simultaneously with the 15-hydroxyprostaglandin dehydrogenase inhibitor. Rather, the 15-hydroxyprostaglandin dehydrogenase inhibitor may be preadministered in a first suppository followed by treatment with the prostaglandin in a second suppository. Pre-treatment or simultaneous treatment with a 15-hydroxyprostaglandin dehydrogenase inhibitor decreases the burning sensation associated with the administration of the prostaglandin. In addition, blocking the PGDH tremendously enhances the absorption and effectiveness of the prostaglandin leading to a remarkably lower dose requirement.

The present suppositories may be manufactured by any standard method known to the art, including but not limited to extrusion, casting, and injection molding. For example, the present suppositories may be prepared by forming, under sterile conditions, an intimate mixture containing the appropriate relative amounts of components (a), (b), and (c) at a temperature above the melting point of component (c) and then forming the suppository of the desired shape by extrusion, casting, or injection molding.

D. Lipophilic Solutions and Suspensions

Lipophilic solutions such as triglycerides with low melting points exhibit several advantages as carriers for the prostaglandin compositions. Prostaglandins are lipid soluble affording a concentrated solution that minimizes the volume necessary for administration. A dropper can be used to easily administer the dosage. Many triglyceride liquids such as triacetin, tricaprin, tricaproin, and others markedly increase the chemical stability of the prostaglandin making storage at room temperature feasible. These solutions are also well tolerated by delicate tissues. Coagents that are not lipid soluble may be suspended in a lipophilic solution of prostaglandin.

Twenty-five (25) mg of PGE-2 were dissolved in 2.5 ml of triacetin. Papaverine HCl (100 mg) as a very fine powder was added, and a suspension was produced on shaking. One drop containing 500 μg of PGE-2 and 2 mg of papaverine HCl may be administered directly to the clitoris or to the surrounding tissues if the

clitoris is not visible and allowed to penetrate the clitoral hood to bring about the desired effect. The dose may be repeated, if needed.

II. PGDH Activity.

A. Pig Clitoral Preparation: Fresh sow external genitalia from sexually mature animals are obtained from a local slaughter house. The excised external genitalia are immediately washed in tap water and then in normal saline. The clitoris is then exposed by retracting the clitoral hood if necessary and the glans clitoridis which corresponds to the free extremity of the clitoris is separated from the rest of the genitalia by sharp dissection. The length in millimeters and the weight in milligrams of the glans clitoridis are measured and recorded. The entire glans clitoridis is homogenized with four volumes of an ice-cold 100 mM potassium phosphate buffer (pH 7.5) containing 1 mM EDTA. Following centrifugation at 15,000 g for 15 minutes, the resultant supernatant fraction is used as the enzyme source of the clitoral mucosa.

B. 15-Hydroxyprostaglandin dehydrogenase (PGDH) Activity Determination: Spectrophotometric analysis:

As a substrate, prostaglandin E_1 is incubated with the pig clitoral enzyme prepared above. The reaction mixture is contained in a total volume of 2.0 ml of the same buffer used above for the preparation of the pig clitoral preparation.

Prostaglandin E_1 (50 microM) and NAD (300 microM) are used as substrates. The reaction is initiated by the addition of the prostaglandin E_1. Incubation is done at 37°C and is terminated by the addition of 0.5 mL of 2NaOH. The oxidation of the prostaglandin is assayed by monitoring the reduction of NAD+ at 340 nanometers in a spectrophotometer. Reaction times are adjusted so that the initial quantity of prostaglandin is oxidized by 50 to 80%.

Radiochemical determination: The same reactions conditions listed for spectrophotometric analysis are used except that (5, 6, 8, 11, 12, 14, 15(n)-^{3}H)-prostaglandin E_2 (specific activity, 171 Ci, mmol) from Dupont de Nemours is used as a typical substrate. Any other tritiated prostaglandin substrate can be utilized in this assay. To terminate the reaction, methanol precipitation (75% volume/volume))

is performed; then, water is added to dilute the methanol to 10 volume percent. Soluble phase extractions are performed using octadecyl 18-C silica cartridges (J.T. Baker, Deventer, Holland). Dried extracts are run on 20 X 20, 60A silica plates using the organic phase of ethyl acetate/acetic acid/isooctane/water (11:2:5:10). Authentic prostaglandin E_2, 15-keto-prostaglandin E_2, and 13, 14-dihydro-15-keto-prostaglandin E_2 are comigrated on separate lanes. After localization of the compounds using phosphomolybdic spray, the silica is scraped, and the respective amounts of prostaglandin E_2 and 15-keto-prostaglandin E_2 are determined by radioactive counting. A mU is defined as that amount of enzyme which oxidizes 1 n mole of prostaglandin E_2 per min at 37°C, pH 7.5. The number of mU PGDH per mm of pig clitoris is then calculated by dividing the total number of mU by the mm of clitoris used to prepare the enzyme.

III. PGDH Inhibitor Activity Determination.

In the context of the present invention, one unit of PGDH inhibition activity is defined as the quantity of inhibitor that prevents one percent of the quantity of prostaglandin present from being oxidized using one of the assays described below. The PGDH may be pig clitoral PGDH as described above or human placental PGDH as described below. In the case of pig clitoral PGDH, the enzyme activity and percent inhibition are preferably measured as described immediately below. In the case of human placental PGDH. the enzyme activity and percent inhibition are preferably measured as described in Anggard, E. And Samuelsson, B. (1966) Ark. Kem. 25, 293-340.

Spectrophotometric: Using the above listed spectrophotometric analytical system for PGDH activity, the inhibitor in question is added to the reaction mixture prior to the addition of the prostaglandin E_1. At termination of the reaction, the quantity of the prostaglandin E_1 degraded is calculated and compared to the reaction without the inhibitor. Percent inhibition is defined as B/A X 100 where

A = nmoles of prostaglandin oxidized without inhibitor.

B = nmoles prostaglandin oxidized with inhibitor.

For example, if A = 50 nmoles and B = 25 nmoles with inhibitor C, then inhibitor C

gives 25/50 X 100 or 50% inhibition in this assay.

Radiochemical Determination: The assay for inhibition is run with and without inhibitor added as listed above in the determination of PGDH activity radiochemically. A given inhibitor is added to the reaction mixture just prior to the addition of the prostaglandin E_1 being analyzed and the analysis performed as listed. The quantity of prostaglandin oxidized is calculated and interpreted as listed above for spectrophotometric analysis of inhibitor activity.

IV. PGDH Activity from Human Placenta

The placenta is one of the richest sources of PGDH containing large quantities of both Type I and II. Placental PGDH can thus be readily utilized as an enzyme source to be used for determining PGDH enzyme inhibitor activity and in deciding upon the relative amounts of prostaglandin and PGDH inhibitor to be incorporated into a unit dose for this invention.

Placenta from a healthy mother with a normal vaginal delivery was placed immediately after delivery on ice. Within 1 hour of delivery, a portion of the placenta (~½) was obtained and rinsed repeatedly with aliquots of ice cold (1-5 °C) homogenate buffer containing 10mM potassium phosphate (pH 7.4), 20% glycerol, 1 mM EDTA, 1 mM dithiothreitol and 100 units heparin per liter until all visible blood and mucous were removed; then the membranes were dissected away and the tissue cut into small pieces. The placenta is extremely rich in blood vessels so the rinsing with buffer was repeated in order to remove as much hemoglobin as practical. Approximately 50 washes were performed. The tissue was then weighed (188.4 grams) and homogenized for 2 minutes at high speed in a commercial blender with 5 volumes of ice cold buffer. Following filtration through cheesecloth, the homogenate was centrifuged at ~ 800 g for 15 minutes, the supernatant filtered successively through a glass fiber filter (retention > 2.3 microns - Sigma Chemical Company - item # F-6269) and finally through a 0.22 micron polyethersulfone membrane filter (Corning Costar Corporation, Cambridge, MA) to produce a crude placental homogenate that is suitable for use as is or may be further purified according to procedures reported in the literature (Mak and Ensor as already cited). Alternatively,

one may take the homogenate from the blender and ultracentrifuge it at 100,000 g for 60 minutes at 0-4 degrees C and use the supernatant as the crude homogenate.

PGDH activity was assayed according to Anggard and Samuelsson (see Anggard, E. And Samuelsson, B. (1966) Ark. Kem. 25, 293-340). However, any other compatible method of measuring PGDH activity including the 2 methods already listed in this report are acceptable. Aliquots (100-200 microliters) of the crude placental homogenate were assayed in a total volume of 1 ml with 200 micromolar PGE2, 50 mM potassium phosphate at pH 7.4, 2.5mM NAD at 37 °C for 45 minutes and the reaction mixture cooled on ice then 1.3 ml of 1 N NaOH added and absorbance of the resultant chromophore read at 500nm in 1 minute on a SPECTRONIC 20 GENESYS spectrophotometer (Spectronic Instruments, Rochester, NY). Blanks were used without the homogenate. Protein concentration was determined using a modified Lowry technique (Catalog # P5656, Sigma Chemical, St. Louis, MO). The absorbance may be used directly or the specific activity of the enzyme calculated. Typical values of PGDH activity obtained were in the range of 4.85 - 6.25 picomoles of 15-ketoprostaglandin E2/ min-ml for homogenate.

Inhibitor activity may be determined by dissolving the chemical to be tested in the assay buffer and pre-incubating the homogenate with the inhibitor for 15 minutes prior to starting the assay listed above by addition of the PGE2. Figure 2 shows examples of the data derived. Fatty acids are not very water soluble so they were dissolved in 95% ethanol and added in aliquots of ~25 microliters. The presence of this amount of alcohol has no effect on enzyme activity. Some sodium salts of fatty acids will precipitate on addition of NaOH. This visible precipitate should be removed by filtration through a 0.22 micron filter prior to measurement of absorbance to ensure accurate results.

One should note that delicate enzyme systems may exhibit a great deal of interassay variability. Additionally, one will not obtain precisely the same results when comparing inhibitor studies that utilize human enzyme obtained from different people especially with an enzyme source that is not highly purified. However, the crude homogenate results should more closely approximate the internal milieu (with both PGDH I and II being present) that an actual dose of this invention will encounter

in administration to a real patient than inhibitor studies that utilize a highly purified PGDH. Using pooled enzyme specimens from several different placentas is one advantageous way to approach this situation. These inhibitor assays should generate approximations of quantities of inhibitor needed per unit dose that will greatly decrease the subsequent need for human testing. The next example lists a greatly simplified method of human screening of dosage combinations that may be fruitfully used in combination with this method to reduce the amount of testing necessary to arrive at an optimum dose combination.

In general, it is desirable to incorporate into a unit dose a quantity of inhibitor that gives > 50% inhibition in this assay. Therefore, unit doses of palmitic acid should have ~ twice or more of the molar quantity of PGE2 used in order to have >50% inhibition of PGDH. Unit doses should have ~2 x or more the molar ratio of oleic acid to PGE2. One can easily use this method to determine the approximate quantities of inhibitor needed per unit dose by simply substituting the inhibitor being tested into this assay in an appropriate solvent and checking to make sure that the chosen solvent does not inhibit the enzyme. In those cases where a different prostaglandin is to be used, it should be substituted for PGE2 in the above assay.

V. Titration of Inhibitor Dose Utilizing Clitoral Artery Blood Flow

Another method of determining the optimum amount of an inhibitor to be used in a unit dose is to make up the inhibitor in various amounts per unit dose in a suppository form. One may then administer these varying doses of inhibitor to a patient and measure the peak systolic blood flow produced in the clitoral artery using ultrasonic techniques. One may easily deduce an appropriate dose for any inhibitor using this technique.

These methods of determining the approximate dose of inhibitor needed in a unit dose of this invention are only one factor to be considered in the final product. For example, some mixtures of PGE-2/ethyl stearate/ and 20:1 oleic acid are not solid at room temperature. Some mixtures of PGE-2/ethyl stearate/ and 20:1 palmitic acid will not melt on the clitoris at normal body temperature.

V. Examples.

Example 1.

A. Two drops of an aqueous solution containing 20μg of prostaglandin E_2, 150 μg of phentolamine hydrochloride, and 3 mg of papaverine hydrochloride in a liposomal solution was applied directly to the clitoris of a 41 year old female with no history of sexual dysfunction, using a dropper. Within one minute the subject reported a pleasurable tingling in her genitals. In the next two to three minutes, increasing sexual feelings were noted in the clitoris and generally throughout the subject's body. In addition, the clitoris became engorged and vaginal lubrication was noted in the same time frame without any stimulation other than the administration of the present composition. The subject reported multiple orgasms upon coitus, which represented an unusual and increased response for her.

B. The same 41 year old female had 2 drops of an aqueous solution containing 125 µg of PGE-2 and 125 µg of phentolamine applied to her clitoris with essentially the same response as in part A.

C. The same female had 3 drops of an aqueous saline solution containing 125 µg of PGE-2 applied to her clitoris and had the same response described in part A but with reduced intensity.

This Example illustrates the efficacy of using a prostaglandin, the additive effect of coadministering a coagent, and the increased activity associated with liposomal mixtures.

Example 2.

Two drops of an aqueous solution containing 50 μg of prostaglandin E_2 and 150 μg of phentolamine hydrochloride was applied directly to the clitoris of a 32 year old female with no history of sexual dysfunction, using a dropper. The subject reported warm tingling sexual feelings in her clitoris within one minute. Clitoral engorgement ensued in the next several minutes along with increasing feelings that the subject identified as most similar to those that she normally experiences with sexual stimulation. The stimulation peaked at around 15 minutes after application of the composition. The subject rated the intensity of her response at eight (8) on a scale of

one (1) to ten (10), with ten being the highest. Both the observable clitoral enlargement and the feeling of sexual excitement were gone within one hour after application of the composition. Repeat dosing at one and a half hours after the first dose gave the same response as the first dose.

EXAMPLE 3.

A pellet containing 70 μg of prostaglandin E_2 and 70 μg of phentolamine hydrochloride distributed in 1.4 mg of MW 1450 polyethyleneglycol (PEG) was applied directly to the clitoris of a 41 year female with no history of sexual dysfunction. The result was similar to those observed in Example 1.

EXAMPLE 4.

A pellet containing 70 μg of prostaglandin E_2 distributed in 1.4 mg of MW 1450 PEG was applied directly to the clitoris of a 41 year old female with no history of sexual dysfunction. The results were similar to those observed in Example 1.

EXAMPLE 5.

Three drops of a liposomal solution containing 150 μg of PGE-2 were applied directly to the clitoris of a 37 year old female with a history of decreased sexual responsiveness. The patient reported warm sexual feelings in her genitalia and had increased genital lubrication and sexual receptiveness. On intercourse. she had an orgasm and reported that she felt that the drops had greatly increased her sexual desire and responsiveness.

EXAMPLE 6.

A 41 year old female with a history of decreased sexual responsiveness and anorgasmia secondary to paroxetine took 50 mg of naltrexone HCl 2 hours before sex and then placed two (2) drops of a liposomal mixture containing 300 μg of PEG-2 on her clitoris. She described tingling sexual feelings in her pelvis and the spreading of the feeling over her body within 1 minute. She noticed a remarkable generalized feeling of sexual receptivity and, upon subsequent coitus, had the best sexual

experience of her life.

EXAMPLE 7.

A 43 year old female related that she had never found sexual relations to be particularly enjoyable, indicating the presence of a primary deficit in arousal. This worsened after surgical menopause following a hysterectomy, and difficulties with lubrication were also noted. Application of a suppository containing 125 μg of PGE-2 and 125 mg of oleic acid in an ethyl stearate base gave a noticeable increase in lubrication and a small increase in sexual responsiveness. Subsequent application of a suppository containing 500 μg of PGE-2, 2.5 mg of oleic acid, and 2.5 mg of papaverine HCl in ethyl stearate at a later date gave markedly increased lubrication, a greater degree of sexual responsiveness for a given stimulus, much faster overall sexual response, and the most intense orgasm that she had ever experienced. This married woman with a single partner reports that her experience with her husband while using this suppository was without a doubt the most satisfying sexual experience of her life. This example illustrates that higher doses of prostaglandin give greater responses, that additional coagents can increase the efficacy of the method, and that both primary and secondary female sexual dysfunctions may be treated by this method.

Obviously, numerous modifications and variations of the present invention are possible in light of the above-given teachings. It is therefore to be understood that, within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

CLAIMS:

1. A method for enhancing female sexual desire and response, comprising topically administering to the clitoris of a subject in need thereof an effective amount of a prostaglandin.

2. The method of Claim 1, wherein said prostaglandin is selected from the group consisting of prostaglandin E-1; prostaglandin E-2; prostaglandin E-3; prostaglandin A-1; prostaglandin B-1; prostaglandin D-2; prostaglandin E-M; prostaglandin F-M; prostaglandin H-2; prostaglandin I-2; 19-hydroxy-prostaglandin A-1; 19-hydroxy-prostaglandin B-1; prostaglandin A-2; prostaglandin B-2; 19-hydroxy-prostaglandin A-2; 19-hydroxy-prostaglandin B-2; prostaglandin B-3; 16,16-dimethyl-Δ^2-prostaglandin E-1 methyl ester; 15-deoxy-16-hydroxy-16-methyl-prostaglandin E-1 methyl ester; 16,16-dimethyl-prostaglandin E-2; 11-deoxy-15-methyl-prostaglandin E-1; 16-methyl-18,18,19,19-tetrahydrocarbacyclin; (16RS)-15-deoxy-16-hydroxy-16-methyl-prostaglandin E-1 methyl ester; (+)-4,5-didehydro-16-phenoxy-α-tetranor-prostaglandin E-2 methyl ester; 11-deoxy-11a,16,16-trimethyl-prostaglandin E-2; (+)-11a,16a,b-dihydroxy-1,9-dioxo-1-(hydroxymethyl)-16-methyl-*trans*-prostene: 9-chloro-16,16-dimethyl-prostaglandin E-2; arboprostil; iloprost; CL 115,347; 16,16-dimethyl-PGE-2; 15(S)-15-methyl-PGE-2; 9-deoxy-9-methylene-16,16-dimethyl-PGE-2, potassium salt: carbaprostacyclin: prostaglandin D_2; 19(R)-hydroxy-PGE-2: 13.14-dihydro-PGE-1; 11β-PGE-2; 19(R)-hydroxy-PGE-1; and 11-deoxy-16,16-dimethyl-PGE-2.

3. The method of Claim 1, wherein said prostaglandin is selected from the group consisting of prostaglandin E-1, prostaglandin E-2, prostaglandin F-2α, prostaglandin D-2, prostaglandin F-1α, and 15-methyl-prostaglandin F-2α.

4. The method of Claim 1, wherein said prostaglandin is applied to said clitoris in an amount of 1 to 5,000 μg.

5. The method of Claim 1, wherein said prostaglandin is applied to said clitoris in an amount of 20 to 2,000 μg.

6. The method of Claim 1, wherein said prostaglandin is prostaglandin E-1, prostaglandin E-2, or prostaglandin E-3.

7. The method of Claim 1, further comprising coadministration of at least one coagent selected from the group consisting of agents which inhibit 15-hydroxyprostaglandin dehydrogenase, ACE inhibitors, nitro vasodilators, alpha blockers, yohimbine, labetalol, carvedilol, bucindolol, phosphodiesterase inhibitors, muscarinic agents, dopaminergic agonists, ergot alkaloids, opiate antagonists, and polypeptide neurotransmitters.

8. A pharmaceutical composition, comprising:

(a) a prostaglandin; and

(b) a pharmaceutically acceptable carrier;

wherein said pharmaceutical composition is selected from the group consisting of (a) aqueous compositions having a pH of 3 to 7; and (b) nonaqueous compositions which further comprise a pharmaceutically acceptable citrate buffer which when dissolved in sufficient water to be 0.01 Molar in citrate affords an aqueous solution having a pH of 3 to 7.

9. The pharmaceutical composition of Claim 8, wherein said prostaglandin is selected from the group consisting of prostaglandin E-1; prostaglandin E-2; prostaglandin E-3; prostaglandin A-1; prostaglandin B-1; prostaglandin D-2; prostaglandin E-M; prostaglandin F-M; prostaglandin H-2; prostaglandin I-2; 19-hydroxy-prostaglandin A-1; 19-hydroxy-prostaglandin B-1; prostaglandin A-2; prostaglandin B-2; 19-hydroxy-prostaglandin A-2; 19-hydroxy-prostaglandin B-2; prostaglandin B-3; 16,16-dimethyl-Δ^2-prostaglandin E-1 methyl ester; 15-deoxy-16-hydroxy-16-methyl-prostaglandin E-1 methyl ester; 16,16-dimethyl-prostaglandin E-2; 11-deoxy-15-methyl-prostaglandin E-1; 16-methyl-18,18,19,19-

tetrahydrocarbacyclin; (16RS)-15-deoxy-16-hydroxy-16-methyl-prostaglandin E-1 methyl ester; (+)-4,5-didehydro-16-phenoxy-α-tetranor-prostaglandin E-2 methyl ester; 11-deoxy-11a,16,16-trimethyl-prostaglandin E-2; (+)-11a,16a,b-dihydroxy-1,9-dioxo-1-(hydroxymethyl)-16-methyl-*trans*-prostene; 9-chloro-16,16-dimethyl-prostaglandin E-2; arboprostil; iloprost; CL 115,347; 16,16-dimethyl-PGE-2; 15(S)-15-methyl-PGE-2; 9-deoxy-9-methylene-16,16-dimethyl-PGE-2, potassium salt; carbaprostacyclin; prostaglandin D_2; 19(R)-hydroxy-PGE-2; 13,14-dihydro-PGE-1; 11β-PGE-2; 19(R)-hydroxy-PGE-1; and 11-deoxy-16,16-dimethyl-PGE-2.

10. The pharmaceutical composition of Claim 8, wherein said prostaglandin is selected from the group consisting of prostaglandin E-1, prostaglandin E-2, prostaglandin E-3, prostaglandin F-2α, prostaglandin D-2, prostaglandin F-1α, and 15-methyl-prostaglandin F-2α.

11. The pharmaceutical composition of Claim 8, wherein said prostaglandin is present in an amount of 1 to 5,000 μg/ml.

12. The pharmaceutical composition of Claim 8, wherein said prostaglandin is applied to said clitoris in an amount of 20 to 2,000 μg.

13. The pharmaceutical composition of Claim 8, wherein said prostaglandin is PGE-1, PGE-2, or PGE-3.

14. The pharmaceutical composition of Claim 8, which further comprises:

(c) an antioxidant selected from the group consisting of citrate salts and tocopherol.

15. The pharmaceutical composition of Claim 14, which is in the form of an aqueous mixture and said antioxidant is sodium citrate.

16. The pharmaceutical composition of Claim 14, which is in the form of a

liposomal solution and said antioxidant is tocopherol.

17. The pharmaceutical composition of Claim 8, which further comprises at least one coagent selected from the group consisting of agents which inhibit 15-hydroxyprostaglandin dehydrogenase, ACE inhibitors, nitro vasodilators, alpha blockers, yohimbine, labetalol, carvedilol, bucindolol, phosphodiesterase inhibitors, muscarinic agents, dopaminergic agonists, ergot alkaloids, opiate antagonists, and polypeptide neurotransmitters.

18. A kit, comprising:

(a) means for containing a prostaglandin or a pharmaceutical composition comprising a prostaglandin; and

(b) means for administering a prostaglandin or a pharmaceutical composition comprising a prostaglandin to the clitoris,

wherein said means for containing contains a prostaglandin or a pharmaceutical composition comprising a prostaglandin.

19. The kit of Claim 18, wherein said prostaglandin is selected from the group consisting of prostaglandin E-1; prostaglandin E-2; prostaglandin E-3; prostaglandin A-1; prostaglandin B-1; prostaglandin D-2; prostaglandin E-M; prostaglandin F-M; prostaglandin H-2; prostaglandin I-2; 19-hydroxy-prostaglandin A-1; 19-hydroxy-prostaglandin B-1; prostaglandin A-2; prostaglandin B-2; 19-hydroxy-prostaglandin A-2; 19-hydroxy-prostaglandin B-2; prostaglandin B-3; 16,16-dimethyl-Δ^2-prostaglandin E-1 methyl ester; 15-deoxy-16-hydroxy-16-methyl-prostaglandin E-1 methyl ester; 16,16-dimethyl-prostaglandin E-2; 11-deoxy-15-methyl-prostaglandin E-1; 16-methyl-18,18,19,19-tetrahydrocarbacyclin; (16RS)-15-deoxy-16-hydroxy-16-methyl-prostaglandin E-1 methyl ester; (+)-4,5-didehydro-16-phenoxy-α-tetranor-prostaglandin E-2 methyl ester; 11-deoxy-11a,16,16-trimethyl-prostaglandin E-2; (+)-11a,16a,b-dihydroxy-1,9-dioxo-1-(hydroxymethyl)-16-methyl-*trans*-prostene; 9-chloro-16,16-dimethyl-prostaglandin E-2; arboprostil; iloprost; CL 115,347; 16,16-dimethyl-PGE-2; 15(S)-15-methyl-PGE-2; 9-deoxy-9-methylene-16,16-dimethyl-

PGE-2, potassium salt; carbaprostacyclin; prostaglandin D_2; 19(R)-hydroxy-PGE-2; 13,14-dihydro-PGE-1; 11β-PGE-2; 19(R)-hydroxy-PGE-1; and 11-deoxy-16,16-dimethyl-PGE-2.

20. The kit of Claim 18, wherein said prostaglandin is selected from the group consisting of prostaglandin E-1, prostaglandin E-2, prostaglandin E-3, prostaglandin F-2α, prostaglandin D-2, prostaglandin F-1α, and 15-methyl-prostaglandin F-2α.

21. The kit of Claim 18, wherein said prostaglandin is PGE-1, PGE-2, or PGE-3.

22. The kit of Claim 18, wherein said means for administering a prostaglandin or a pharmaceutical composition comprising a prostaglandin to the clitoris is capable of delivering said prostaglandin to said clitoris in an amount of 1 to 5,000 μg.

23. The kit of Claim 18, wherein said means for administering a prostaglandin or a pharmaceutical composition comprising a prostaglandin to the clitoris is capable of delivering said prostaglandin to said clitoris in an amount of 20 to 2,000 μg.

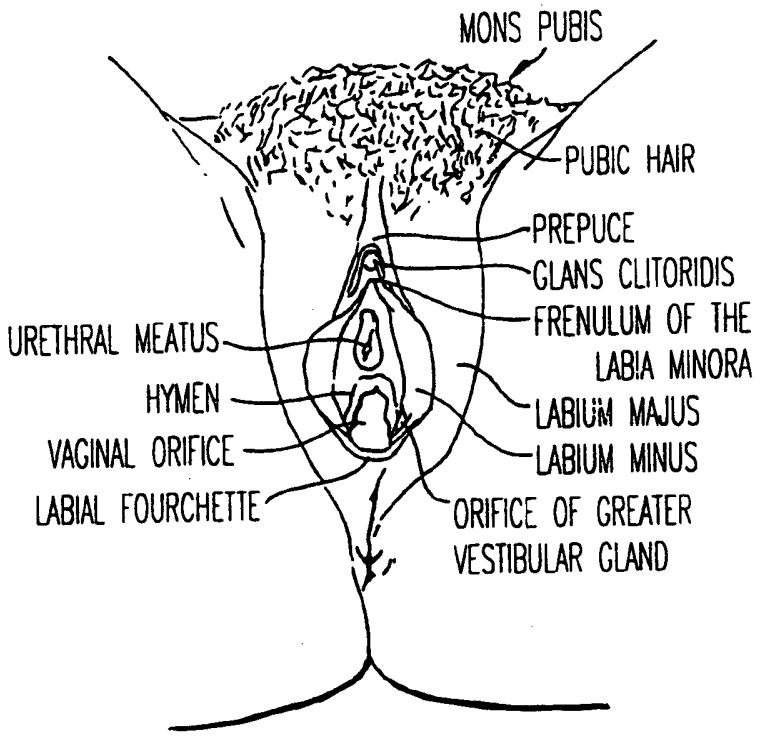

MONS PUBIS
PUBIC HAIR
PREPUCE
GLANS CLITORIDIS
FRENULUM OF THE LABIA MINORA
LABIUM MAJUS
LABIUM MINUS
ORIFICE OF GREATER VESTIBULAR GLAND
URETHRAL MEATUS
HYMEN
VAGINAL ORIFICE
LABIAL FOURCHETTE

FIG. 1

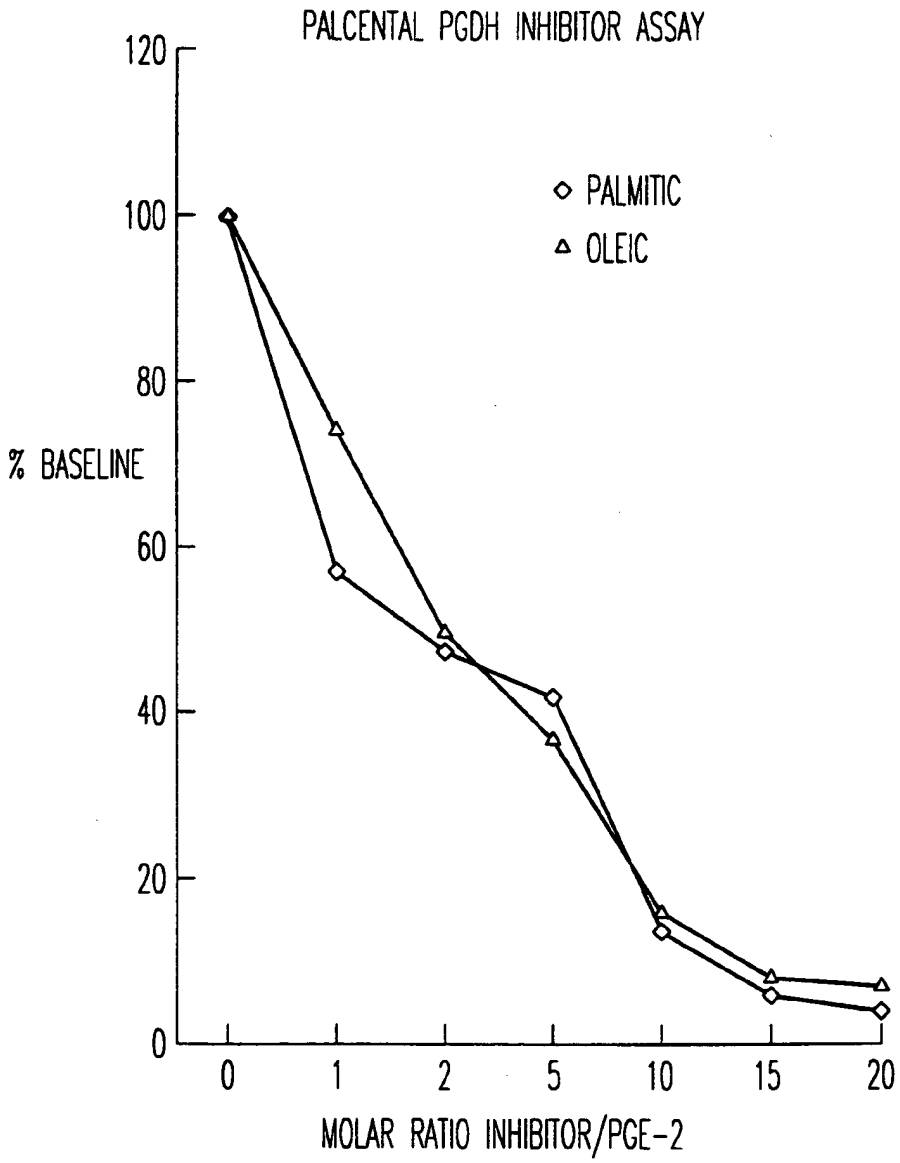

PALCENTAL PGDH INHIBITOR ASSAY
120
100
80
60
40
20
0
% BASELINE
◇ PALMITIC
△ OLEIC
0
1
2
5
10
15
20
MOLAR RATIO INHIBITOR/PGE-2

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/21631

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/19, 31/557
US CL :514/573

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/573

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, USPATFULL, HCAPLUS, EMBASE- prostaglandins and prostaglandin degrading enzyme inhibitors for the treatment of male and/or female sexual dysfunction

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ROY, A.C. et al. Prostaglandin 15-hydroxydehydrogenase Activity in Human Penile Corpora Cavernosa and its Significance in Prostaglandin-mediated Penile Erection. British Journal of Urology. 1989, Vol. 64, pages 180-182, see entire document.	1-23
Y	US 5,576,290 A (HADLEY) 19 November 1996, see entire document, especially col. 2, lines 21-41 and col. 4, lines 40-52.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 21 DECEMBER 1998	Date of mailing of the international search report 19 JAN 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer M. MOEZIE Telephone No. (703) 308-1235

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